IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	M. Vijay Kumar
Serial No.	:	10/077,435
Filing Date	:	February 15, 2002
Title	:	TREATMENT OF PROSTATE CANCER
Examiner	:	DAVIS, MINH TAM B
Group Art Unit	:	1642

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, M. Vijay Kumar, do hereby declare the following:

1. I am the sole inventor of the claimed inventions disclosed in the above-referenced U.S. Patent Application Serial No. 10/077,435.

2. I am employed as an Associate Professor at the Medical College of Georgia. In conjunction with my ongoing research responsibilities, I have been actively engaged in research relating to developing chemotherapeutic treatments for cancer, and in particular, prostate cancer for over 15 years.

3. I have reviewed the Office Action mailed April 21, 2006, in the above-referenced patent application and, in particular, the Examiner's rejection of claims under 35 U.S.C. § 103(a), at pages 2-12 of the Office Action.

4. I have also reviewed each of the following references cited by the Examiner: Bonavida, B. et al., 1999, Oncology 15(4):793-802; Yu et al, 2000, Cancer Res., 60:2384-2389; Gliniak, B., et al., 1999, Cancer Res., 59:6153-6158; Fathy El Etreby et al., 2000, The Prostate 42: 99-106; and Kiode, S.S., et al., J. Reproductive Medicine, 1998, 43:551-560.

5. I have also reviewed the Amendment and Response filed herewith (hereinafter "the Response"), and believe that the references cited by the Examiner do not, either alone, or in combination, describe, teach, or suggest my invention for at least the reasons cited in the Response.

6. I was aware of the art relating to the use of antiprogestins as chemotherapeutic agents and have collaborated with many of the researchers listed as authors on the El Etreby paper (Fathy El Etreby et al., 2000, The Prostate 42: 99-106), and in particular, Dr. Yayun Liang and Dr. Ronald Lewis. After the retirement of Dr. El Etreby, Dr. Liang worked in my laboratory as a post-doctoral fellow. At the time of my invention, it was believed that Mifepristone worked at the level of either the progesterone or the glucocorticoid receptor. Thus, the idea that Mifepristone might interact with the TRAIL pathway was not suggested by Mifepristone research taking place at the time.

7. The following references cited by the Examiner, Bonavida, B. et al., 1999, and Gliniak, B., et al., 1999, describe chemotherapeutic agents that act in a very different manner than antiprogestins act in prostate cancer, and one would generally not expect to use such compounds interchangeably. For example, actinomycin D works as a generalized anti-transcription agent and CPT-11 acts to inhibit DNA topoisomerase. In contrast, antiprogestins work by binding to either the androgen or progesterone receptor to then specifically increase expression of death receptors in prostate cancer.

8. The discovery that a Tumor necrosis factor α - Related Apoptosis Inducing Ligand (TRAIL) polypeptide, and an antiprogestin, such as Mifepristone, provides a composition that provides a synergistic effect, to reduce tumor cell survival in amounts that is greater than the additive effect of both agents as shown in my patent application, was very surprising, both to me and others in the field. These results were surprising because at the time of my invention, it was suggested by published reports that LNCaP cells are resistant to TRAIL as the oncogene AKT is constitutively phosphorylated in these cells. Thus, it was believed that phosphorylated AKT promotes cell proliferation

and results in LNCaP cells being resistant to apoptosis. However, our results demonstrated that phosphorylated AKT notwithstanding, we were able to induce significant apoptosis by combining Mifepristone and TRAIL.

9. The finding that Mifepristone could act on the TRAIL pathway to sensitize cells to TRAIL was also unexpected. Although it had been shown that TRAIL can, in some circumstances, induce low levels of apoptosis in prostate cancer cells, it was entirely unexpected that Mifepristone would be able to act via the TRAIL pathway to increase TRAIL receptors and TRAIL-mediated apoptosis. By acting on the TRAIL pathway, Mifepristone is able to increase cell death in a very specific manner, unlike the chemotherapeutic agents in the references (Bonavida and Gliniak) that were cited by the Examiner.

10. The finding the Mifepristone and TRAIL interact in a synergistic manner was very surprising. Although Mifepristone was believed to act as mild inducer of apoptosis, because TRAIL and Mifepristone both act on the TRAIL pathway, we expected at best, a marginal, additive, increase in apoptosis.

11. Also, the invention described in my patent application fulfills a long-felt need for a therapy that can target both hormone-sensitive and hormone-independent cells to induce apoptosis. Prostate cancer is one of the most commonly diagnosed malignancies in men, and a leading cause of cancer-related death. By providing a composition utilizing low doses of TRAIL and an antiprogestin, potentially toxic effects of either compound are avoided. Also, prostate cancer is a multi-focal disease with clones of androgen-sensitive and androgen-refractory cells. Although androgen depletion therapy often results in regression of the tumor, a small number of androgen-sensitive prostate cancer cells are often able to develop into androgen-independent cells by an as yet unknown mechanism. Also, the androgen sensitive cells can be highly aggressive in their rate of growth. Thus, there is a need to be able to target both types of cells, androgen-sensitive and androgen-insensitive, in cancer therapy. I am not aware of any

other combination therapy prior to my invention that was so effective at killing both androgen-sensitive and androgen-insensitive cells.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

July 21, 2006

M. Vijay Kumar, Ph.D.